SYNTHESIS OF PHILANTHOTOXIN ANALOGS WITH BULKY HEADS INCLUDING PORPHYRINS. SELF-ASSEMBLY MONITORED BY CIRCULAR DICHROISM

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Abstract-Philanthotoxin (PhTX) analogs with bulky bis-iminodibenzyl and porphyrin head groups have been prepared. Exciton coupled CD studies show that dependent on the hydrophobicity of the head group PhTX analogs may get amphiphilic properties forming micelles in aqueous solution.

We dedicate this paper to the memory of Yoshi Ban

1. Introduction: Eldefrawi *et al.*[1] and Piek *et al.*[2] isolated and characterized philanthotoxin 433 (PhTX-433) from *Philanthus triangulum F.*, a solitary Sahara Desert digger wasp that preys on honeybees and blocks the quisqualate-sensitive post-junctional glutamate receptor (qGluR).[3] This neurotoxin belongs to the large family of polyamine-amide toxins which inhibit both the ionotropic glutamate receptors (GluRs) in post-synaptic neurons and the conductance of cation channels gated by nicotinic acetylcholine receptors (nAChRs).[4]

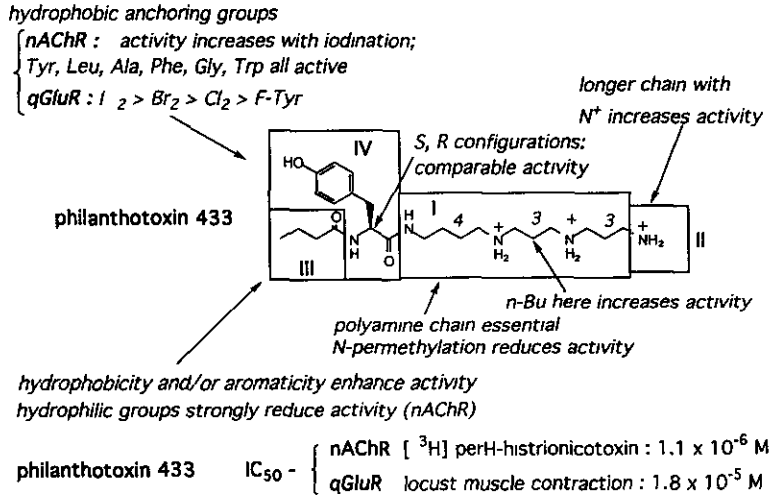


Figure 1 : Summary of SAR studies of philanthotoxin 433 analogs with insect GluR and nAChR.

In order to investigate the channel blocking potencies of PhTX analogs against both the nAChR and GluR, structure relationship studies with 100 synthetic analogs have been performed by dividing the molecule into four regions, and structurally changing the regions selectively or simultaneously; the results are collectively summarized in Figure 1.
Since none of the GluRs are as yet available in quantities sufficient to perform molecular level structural studies of ligand/receptor binding, recent and current ongoing cross-linking studies are being performed with nAChR. Recent photoaffinity studies using the radioactive PhTX analog, N_3-Ph-$^{125}I_2$-PhTX-343-Lys has shown that the toxin binds as depicted in Figure 2.[5] The 270 KDa receptor consists of 5 subunits (α, α, β, υ, δ) arranged centrosymmetrically around the gate, which when opened by attachment of acetylcholine to the agonist receptor, becomes permeable to potassium and sodium ions. In the absence of the 43 KDa protein located on the cytoplasmic side of the receptor, the PhTX analog crosslinked to all five subunits of purified nAChR. In contrast, in the presence of the 43 KDa protein, only the α subunit was selectively labeled. Proteolysis of the receptor after crosslinking indicated that it was the hydrophobic end (head) of the PhTX-433 analog that was bound to the cytoplasmic loops of the α-subunit. However, under the conditions of the crosslinking studies,[5] the toxin had access to both the cytoplasmic as well as the synaptic sides of the nAChR; hence the mode of attachment *in vivo* is unknown at this stage.

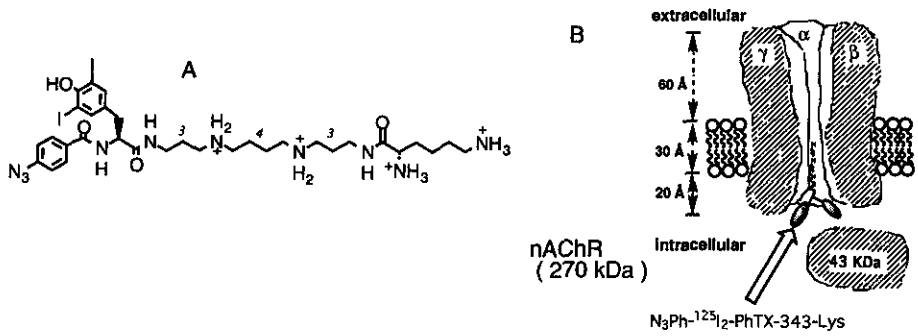


Figure 2: (A). Radioactive and photolabile PhTX: N_3Ph-$^{125}I_2$-PhTX-343-Lys. (B). Orientation of the PhTX analog in open nAChR gate.

Elucidation of the *in vivo* mode of entry of the toxin into the open gate as well as its mode of attachment to the receptor is a focal point in understanding the mode of action PhTX on nAChR and eventually the GluRs. One approach to investigate the crucial mode of entry of the toxins into their binding sites is to compare the binding of analogs carrying very bulky head groups with that with smaller head groups (Figure 3). Conventional PhTX analogs can enter the receptor from the synaptic side and either settle in a head-out orientation (Figure 3A), or flip over and settle in a head-in orientation (Figure 3B). If the head groups of PhTX analogs is larger than the 10-12 Å constriction of the open gate of nAChR,[6,7] they can only block the channel in a head-out configuration (Figure 3C). These analogs will be assayed by using the "black lipid membrane"[8] technique or by electrophysiology using electrocytes enriched in nAChR isolated from skate (*Raja*) electric organ; *in the latter assay, the analogs can only enter the receptor from the extracellular synaptic side.* Therefore, if the toxin functions *in vivo* in a head-out orientation, the bulky analog will assay positively; on the other hand, if the toxin has to be bound to the receptor in a head-in orientation, the electrocyte assay will be negative. Upon completion of these experiments, radiolabeled PhTXs with photolabile moieties will be crosslinked and the *in situ* labeling site will be sequenced.

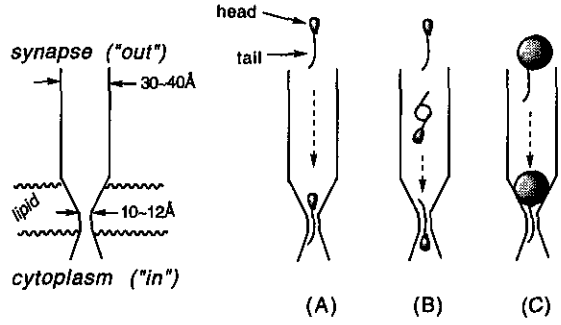


Figure 3: PhTXs are administered *in vivo* to skate (*Raja*) electrocytes (see above). (A) PhTX settles in head-out direction. (B). PhTX flips over and settles in head in direction. (C) Bulky-head PhTXs can only settle in head-out direction.

Thus PhTX analogs with a bulky bis-iminodibenzyl head group (16-17 Å) and various polyamine tails have been prepared in order to ascertain that the hydrophilic tail is long enough to enter the open gate (Figure 4A). Large porphyrin moieties have also been linked to polyamine chains to form PhTX porphyrin analogs for additional SAR-studies by spectroscopic methods, i.e. circular dichroism (CD). Hydrophilic and hydrophobic porphyrin heads (*ca.* 16 Å) have been linked to a constant polyamine tail. Preliminary CD-studies show that with increasing hydrophilicity of the head group, PhTX analogs can become amphiphilic, forming micelles in aqueous solution. PhTX-micelles most probably will not bind to nAChR. But their expected inactivity will not be caused by a "bad fit". Therefore micelle formation of amphiphilic PhTX analogs may afford misleading SAR-results. In Section 3 we demonstrate that CD spectroscopy is a powerful tool to examine the amphiphilicity of chiral PhTX analogs, and therefore to select suitable toxins for SAR-studies.

2. Synthesis of Philanthotoxin Analogs with Bulky Heads: The bis-iminodibenzyl PhTX analogs (**1-4**) (Figure 4B) were synthesized by formation of amide linkage between spermine and the polyamines (**5-7**) (Scheme 1, 2) to the bulky head group (**8**) (Scheme 3). Polyamine (**5**) (Scheme 1) was synthesised by Michael addition of diamine (**9**) to acrylonitrile giving nitrile (**10**). BOC protection (**11**) and reduction of the nitrile by $Pd(OH)_2/C$ catalyzed hydrogenolysis at 50 psi yielded the amine (**12**). Repetition of Michael addition to acrylonitrile (**13**), BOC protection (**14**) and reduction gave the 334-polyamine (**15**). Elongation of **15** performed by Michael addition (**16**), BOC protection (**17**) and reduction afforded the selectively protected 3334-polyamine (**5**).[10]

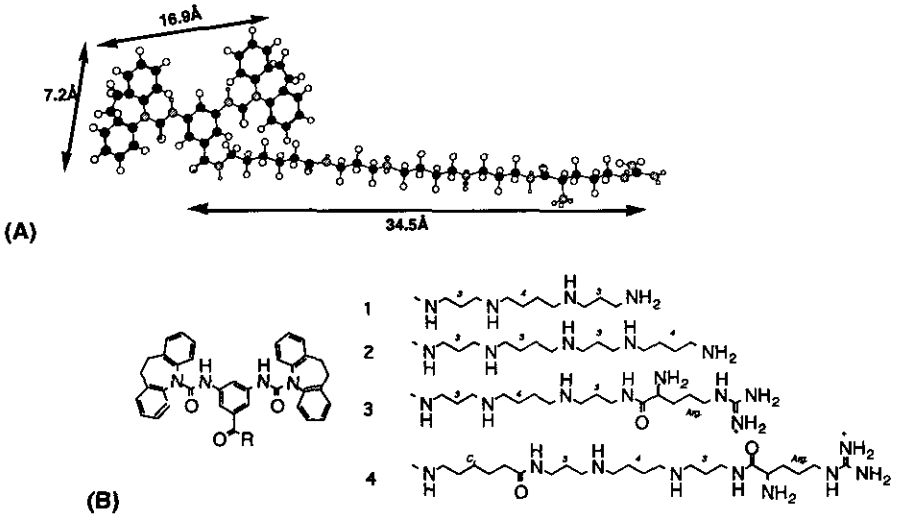
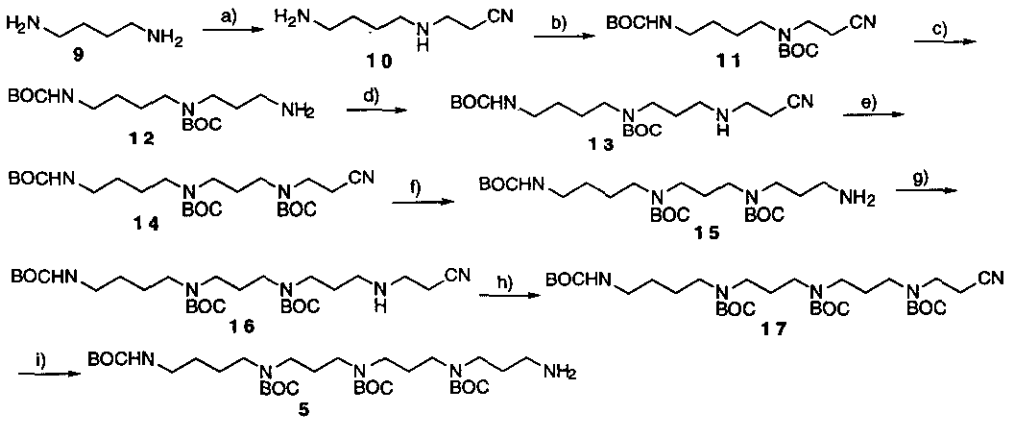


Figure 4: (A) Dimensions of **4** as estimated by MacroModel 4.5.[9] (B) Four bulky PhTX analogs with varying polyamine chainlengths.

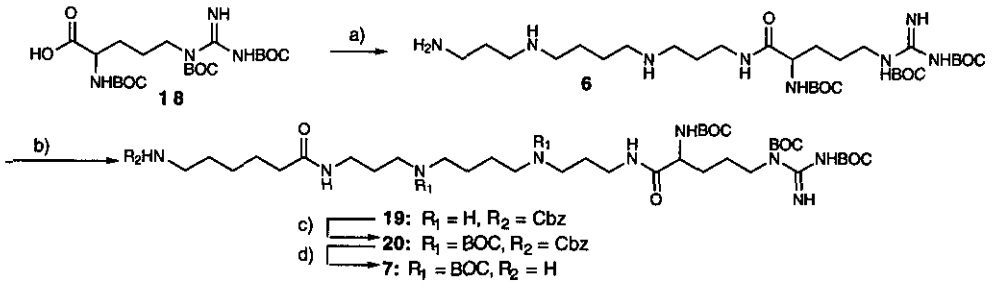


a) acrylonitrile, MeOH, room temperature, overnight, 50%; b) $(BOC)_2O$, Et_3N, CH_2Cl_2, room temperature, 5 h, 95%; c) H_2, 20% $Pd(OH)_2/C$, AcOH, 50 psi, room temperature, 2 h, 85%; d) see a), 99%; e) see b), 95%; f) see c), 98%; g) see a), 85%; h) see b), 95%; i) see c), 91%.

Scheme 1

The 343-Arg polyamine (**6**) was prepared by the activation of tri-BOC-Arg (**18**) with CDI[11] to generate N-acylimidazole as an intermediate, which was added *in situ* to spermine (Scheme 2). The one-pot reaction was used here instead of the conventional route of coupling the activated ester to spermine, which is more time consuming and gives a lower yield. Elongation of 343-Arg (**6**) with Cbz protected aminocaproic acid gave **19**; BOC protection of the secondary amines (**20**) and removal of the Cbz group yielded the polyamine (**7**). The bis-iminodibenzyl head (**8**) was prepared by methylation of diaminobenzoic acid (**21**) with methanol and thionyl chloride, giving **22**, followed by coupling of iminodibenzyl-5-carbonyl chloride to the amine groups to yield ester (**23**) (Scheme 3). The later step requires long reflux

to achieve decent yield regardless of the solvent used. The low yield of the coupling (*ca.* 24%) is presumably due to hindrance of the big aromatic ring; however, usage of a large excess of iminodibenzyl-5-carbonyl chloride led to improvement of the yield to 75%. Hydrolysis of the methyl ester with LiOH in THF/H_2O mixture afforded acid (**8**). Final coupling of the head group (**8**) with spermine, 3334-polyamine (**5**), 343-Arg (**6**), and C_6-343-Arg (**7**) in the presence of CDI afforded the bulky headed PhTX analogs (**1-4**), respectively. Activity tests of **1-4** for the determination of the optimal polyamine chainlenght for the orientation studies are undergoing.



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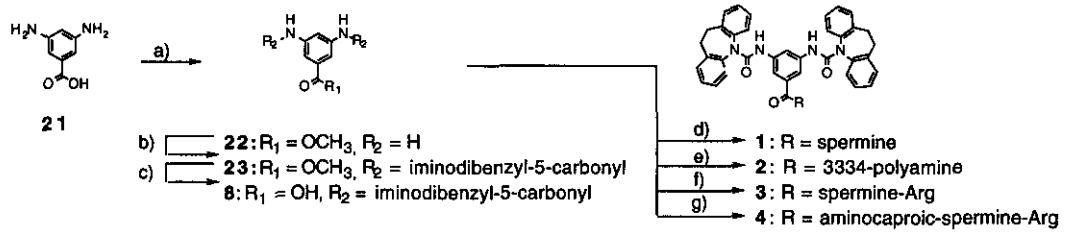
a) CDI, CH_3CN, spermine, room temperature, 1.5 h, 86%; b) 6-Cbz-aminocaproic acid, CDI, CH_3CN, room temperature, 2.5 h; c) $(BOC)_2O$, CH_3CN, room temperature, 2 h, 56%; d) H_2, 10% Pd/C, MeOH, room temperature, 8 h, 96%.

Scheme 2

The hydrophobic triphenyl porphyrin (**24**) (TPP) was synthesized based on published procedures[12] by refluxing 4-carboxymethyl-benzaldehyde (**25**), benzaldehyde (**26**), pyrrole (**27**), and zinc acetate in propionic acid (Scheme 4). Since crystallization from the reaction mixture gave only a small amount of product mixture, the solvent was removed first by reduced pressure, then the product mixture was pre-purified before the final oxidation with DDQ and removal of zinc. This modification finally afforded ester (**28**) in 8% yield, which was hydrolyzed to give porphyrin (**24**). The hydrophilic porphyrin chromophore (**29**)[13] was prepared similarly using nicotinic aldehyde (**30**) instead of **26**. In the ^1H nmr of pure ester (**29**) (as well as **31**) all signals are multiplied with increasing high field shifts. This splitting of the signals can be accounted for by intermolecular complexion of the zinc by a pyridine of another zinc tripyridyl porphyrin (ZnTPyP); this exposes the protons of the ligand porphyrin to the ring current of the zinc porphyrin, giving rise to the observed high field shifts.



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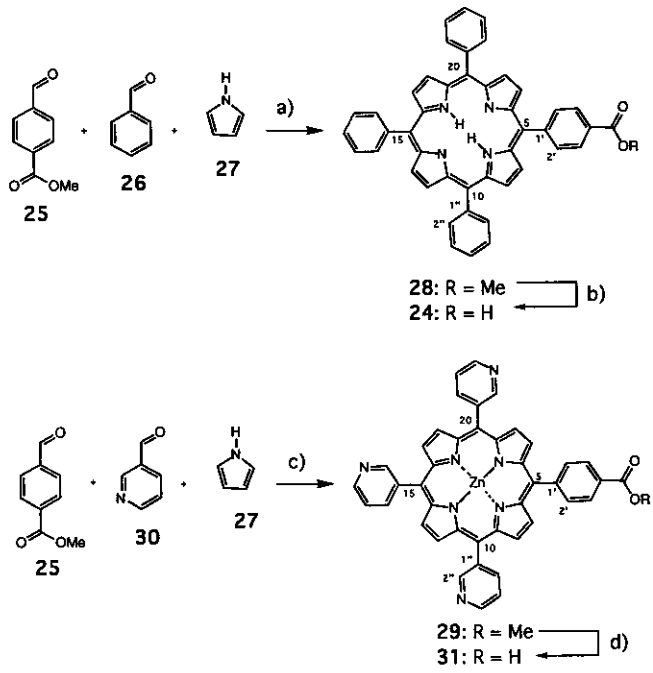
a) $COCl_2$, MeOH, 40°C, 4 h, 94%; b) iminodibenzyl-5-carbonyl chloride, Et_3N, CH_2Cl_2, reflux, overnight, 72%; c) LiOH, THF/H_2O, room temperature, overnight, 98.6%; d) 1. CDI, spermine, CH_3CN, room temperature, 2 h; 2. TFA, CH_2Cl_2, 1.5 h, 35%; e) 1. CDI, **5**, CH_3CN, room temperature, 2 h; 2. TFA, CH_2Cl_2, 1.5 h, 88%; f) 1. CDI, **6**, CH_3CN, room temperature, 2 h; 2. TFA, CH_2Cl_2, 1.5 h, 91%; g) 1. DCC, **7**, room temperature, 4 h, 2. TFA, CH_2Cl_2, room temperature, 1.5 h, 99%.

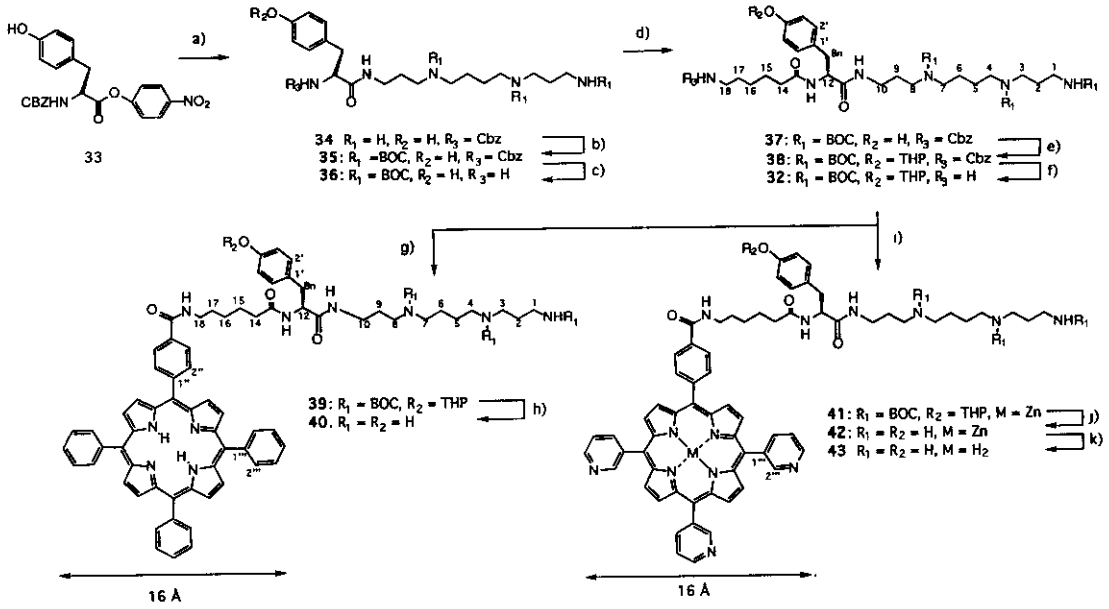
Scheme 3

In order to synthesize selectively protected C_6-Tyr-343 (**32**), spermine was coupled to L-Tyrosine-p-nitrophenol ester (**33**) to give Tyr-343 (**34**) (Scheme 5). BOC protection (**35**) and Cbz removal by catalytic hydrogenolysis[14] gave amine (**36**), which was condensed with Cbz-6-aminocaproic acid to afford C_6-Tyr-343 (**37**). THP-protection of the free hydroxyl group (**38**) and removal of the Cbz yielded the primary amine (**32**). Coupling of the hydrophobic porphyrin (**24**) and polyamine (**32**) afforded the amide (**39**), which was deprotected to give the final TPP-PhTX (**40**). The same sequence was preformed using the hydrophilic ZnTPyP (**41**).



a) 1. $Zn(OAc)_2$, propionic acid, reflux, 4 h; 2. DDQ, pyridine, CH_2Cl_2, room temperature, 1 h; 3. 18% aq HCl/CH_2Cl_2 1:1, room temperature, 5 min, 7.5%; b) 2N aq. KOH/EtOH 2:1, reflux, 4 h, 86%; c) 1. $Zn(OAc)_2$, propionic acid, reflux, 4 h; 2. DDQ, pyridine, CH_2Cl_2, room temperature, 1 h, 5.4%; d) 2N aq. KOH/EtOH 2:1, reflux, 4 h, 88%.

Scheme 4



a) spermine, THF, room temperature, 6 h, 80%; b) $(BOC)_2O$, CH_2Cl_2, room temperature, 4 h, 75%; c) H_2, 10% Pd/C, MeOH, room temperature, 8 h, 84% ; d) Cbz-6-aminocaproic acid, DCC, CH_2Cl_2, room temperature, 3 h, 87%; e) DHP, PPTS, CH_2Cl_2, room temperature, 2 h, 92%; f) see c), 76%; g) **24**, EDC, DMAP, CH_2Cl_2, room temperature, 8 h, 54%; h) 1. TFA, CH_2Cl_2, room temperature, 1 h; 2. TFA, EtOH, room temperature, 8 h, 96%; i) **31**, EDC, DMAP, CH_2Cl_2, room temperature, 8 h, 61%; j) 1. TFA, CH_2Cl_2, room temperature, 1 h; 2. TFA, EtOH, room temperature, 8 h, quant.; k) MeOH/conc. HCl 2:1, room temperature, 1 min, quant.

Scheme 5

3. Micelle formation of amphiphilic PhTX porphyrin analogs in aqueous solution: Binding studies of PhTX analogs to nAChR or GluR have to be performed in aqueous solution. Therefore, the water solubility is a crucial point of PhTX analogs. Most philanthotoxins behave like detergents because of the hydrophobic head groups and the hydrophilic polyamine tail. Since micelle formation would lead to inactivation, water solubility becomes an important attribute. If the hydrophobic heads in PhTX analogs have intensely absorbing chromophores, like the porphyrin analogs, micelle formation could lead to observation of exciton coupled CD because the hydrophobic heads would be stacked in the core of the micelle, with the hydrophilic polyamine tails exposed to the aqueous phase. CD spectroscopy therefore can be used to select suitable PhTX analogues for SAR-studies.

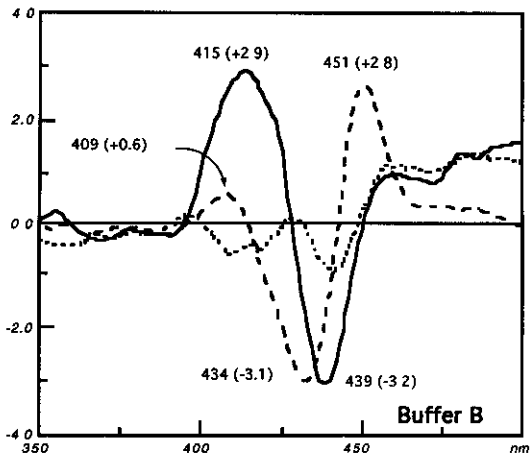


Figure 5: The CD of the porphyrin-PhTX **40** (solid), **42** (dashed), and **43** (dotted), in buffer B.

TPP-PhTX (**40**) is readily dissolved in buffer B by brief sonification. The CD spectra exhibit split Cotton effect with similar intensities around the porphyrin 420 nm Soret band (Figure 5) due to coupling between the stacked porphyrin chromophores chirally perturbed by the tyrosine. From the negative sign of the exciton couplet, and from the recently assigned direction of the interacting transition moments,[15] it follows that the sense of twist between two interacting porphyrins is as shown in Figure 6A, i.e., the electric transition moments of two porphyrin chromophores consititute a negative twist. This interpretation is supported by other data such as the intermolecular chiral stacking of acridines,[16] anthocyanines,[17] pyrenyls,[18] and amphotericin B[19] in polar solutions.

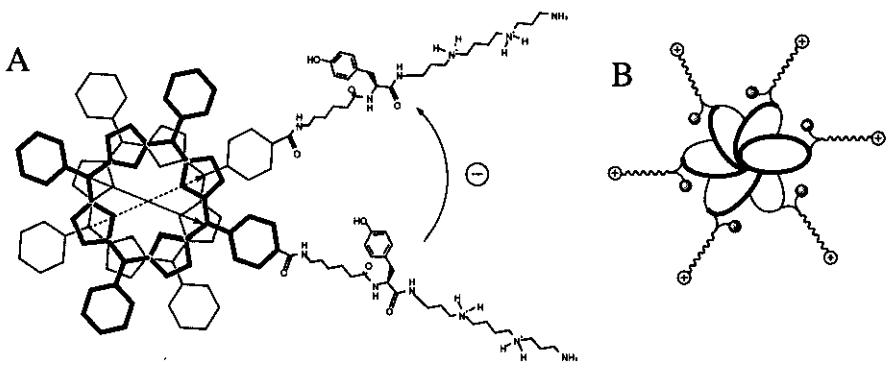


Figure 6: (A) Orientation of porphyrins in a dimeric unit of stacked TPP-PhTX (**40**). The porphyrin skeleton is drawn schematically for simplicity. The arrows in the porphyrin core indicate the direction of the coupling transition moments, whose negative twist is reflected in the CD. (B) Schematic presentation of a possible structure of the micelle formed by **40** in aqueous solution.

There is no direct spectroscopic evidence regarding the degree of oligomerisation, but we assume that the porphyrin-PhTX (**40**) forms micelles surrounded by the hydrophilic polyamine (Figure 6B). The chiral bilayer forming ammonium amphiphiles containing biphenyl chromophores and alanine, respectively, prepared by Kunitake and coworkers, exhibit similar CD enhancement upon aggregation (micelle formation);[20] the chiral superstructure of this bilayer proposed on the basis of CD was later confirmed by electron micrograph to be helical.[21]
Since such micelle formation will necessarily reduce the activity of the PhTX analog (in fact **40** *is 100-fold less active* than PhTX),[22] the ZnTPyP-PhTX (**42**) with a more hydrophilic porphyrin moiety was prepared. The CD spectrum of **42** in buffer B (dissolved by brief sonification) shows a Cotton effect, whose sign is opposite to that of **40**, i.e., the hydrophobic porphyrins now form a right-handed helical core (Figure 5). This geometrical change is easily explained by intermolecular pyridine zinc complexes. Pyridine zinc porphyrin complex formation in the micelle of **42** in buffer B is determined by the increased extinction of the bathochromically shifted α-band at 606 nm in the absorption spectrum (not shown), giving an α/β-ratio of 0.61 (in MeOH: α: 595 nm, α/β = 0.22, no CD).[23] The majority of X-ray crystallographic and nmr structure determinations of pyridine zinc porphyrin complexes have shown the ligand plane to be perpendicular to the porphyrin plane, the projection of the ligand plane on the N-Zn-N axis being less than 26°, with a pentacoordinated zinc *ca.* 0.3 Å out of plane (Figure 7A).[24] The stability of this conformation, which may include Zn-N bonding of the d_{xz} and d_{xy} of Zn and the π and/or π* of pyridine, has been illustrated by Bobrik and Walker.[24a] They linked a pyridine ligand covalently to a ZnTPP with a bridge short enough to force the pyridine plane on the 5-15 porphyrin axis; but surprisingly the X-ray structure of this complex exhibited a strained conformation of the bridge, the ligand plane still being on the N-Zn-N axis. This stable structure of zinc pyridine complexes leads us to conclude that the ZnTPyP-PhTX (**42**) can not dimerize in the manner depicted in Figure 7B where two molecules are associated through *two* Zn-N bonds. The porphyrins could possibly be arranged as shown in Figure 7C, giving rise to the positive exciton coupled CD. However, there is no evidence showing whether the pyridine ring that is vicinal or diagonal to the PhTX substituent coordinates. As the possibility of a "doubly-bridged" dimerization (Figure 7B) can be excluded, the exclusive complex formation detected by UV proves the occurrence of *oligomerization*, i.e. *micellization* of **42** in buffer B; and the structure of this micelle must be the right-handed analog of the micellar structure of **40** shown in Figure 6B.
Removal of the zinc gave the TPyP-PhTX (**43**) It was *soluble in buffer B without sonification* and gave rise to an almost complete disappearance of the Cotton effect. The replacement of the three phenyl groups in TPP-PhTX (**40**) by the more hydrophilic pyridine groups in TPyP-PhTX (**43**) leads to the disappearence of micelle formation in aqueous solution and almost complete dissolution of **43**, which can be further improved by methylation of the pyridines in **43**.

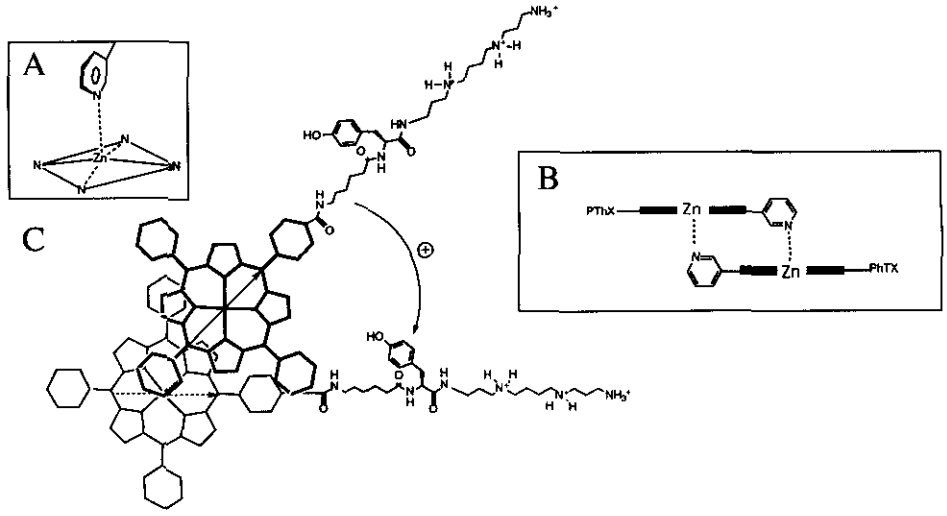


Figure 7: (A) The structure of pyridine zinc porphyrin complexes.[24] (B) Schematic presentation of a "doubly-bridged" dimer of ZnTPyP-PhTX (**42**). (C) The orientation of the porphyrins in the dimer of ZnTPyP-PhTX (**42**) containing one Zn-pyridine bond. The porphyrin skeleton is drawn schematically for clarity. The arrows in the porphyrin core indicate the direction of the coupling transition moments, whose positive twist is reflected in the CD spectrum.

In conclusion we have shown by exciton coupled CD that hydrophobic head groups lead to amphiphilic PhTX analogs such as TPP-PhTX (**40**) or ZnTPyP-PhTX (**42**), respectively, which form helical structured micelles in aqueous solution. Such amphiphiles are not suited for bioactivity studies. It has been shown that an increase in the hydrophilicity of the (porphyrin) head group such as TPyP-PhTX (**43**) supresses micellization. *This study, which has yielded the water-soluble* pyridine porphyrin PhTX analog (**43**), demonstrates the usefulness of CD in designing further water-soluble bioactive philanthotoxins as well as in tertiary structural studies of the mode of action and binding.

EXPERIMENTAL SECTION

Material and Methods. Reagents and starting materials were purchased from common commercial suppliers were used as received. Solvent CH_2Cl_2, and reagent Et_3N were distilled at atmospheric pressure over CaH_2, THF was distilled over Na. CH_3CN, MeOH, and EtOH were dried over molecular sieves (4 Å). All reaction were performed in dry glassware under argon. Reactions were followed by thin-layer chromatography (Tlc) on Merck (0.25 mm) glass-packed, precoated silica gel plates (60 F_{254}) or Whatman aluminia sheets, coated with silica gel (4 x 10 cm, 250 mm, UV_{254}). Preparative Tlc (pTlc) were performed on Analtech (500 microns, 20 x 20 cm, silica gel) or Whatman Tlc plates (K5F, 20 x 20 cm, silica gel 150 Å, 250 mm, UV_{254}). Column chromatography was carried out using ICN silica gel (32-63 mesh). Hplc purification was performed using a Waters hplc system equipped with a Waters 600 E Multisolvent Delivery System, a Waters 600 Controller and a Waters 996 Photodiode Array Detector using the Millennium 2010 software for data processing. Infrared (ir) spectra were obtained as CCl_4 solution using a NaCl microcell on a Perkin Elmer 1600 FT-ir spectraphotometer. Melting points (mp) were measured on a Thomas Capillary Melting Point Apparatus (uncorrected). ^1H nmr and ^{13}C nmr spectra were recorded on Varian VXR400 or Varian VXR300, and reported in parts per million (ppm) using residual proton solvent peaks of either $CDCl_3$ at 7.24 ppm or CD_3OD at 3.30 ppm as an internal standard, with coupling constants (*J*) in Hertz (Hz). ms(CI)(NH_3) spectra were obtained on a NERMAG R10-10 while low and high resolution ms(FAB) (3-nitrobenzyl alcohol matrix) spectra were obtained with a JOEL JMS-DX303 HF, ms are expressed as m/z. In most cases the $M + H^+$ or $M + NH_4^+$ were strongest peaks; only the former peaks are given. uv/vis spectra were recorded in aqueous solution on a Perkin-Elmer Lambda 4B spectraphotometer, and reported as λ_{max} [nm]($\Delta\varepsilon_{max}$ [$lmol^{-1}cm^{-1}$]). cd spectra were recorded in aqueous solutions on a JASCO J-720 spectrapolarimeter driven by a JASCO DP700N data processor, respectively, and reported as λ_{max} [nm] ($\Delta\varepsilon_{max}$ [$lmol^{-1}cm^{-1}$]). Smoothing and other manipulations of spectra were carried out with a software developed in house: DFT (Discrete Fourier Transform) procedure for smoothing.

***N*-(Cyanoethyl)-1,4-butyldiamine (10).** To 20 ml of dry MeOH solution containing **9** (3.0 ml, 29.84 mmol) was injected acrylonitrile (1.96 ml, 29.84 mmol) in 5 ml MeOH by syringe pump (1/100) over 3 h, and the mixture was stirred overnight. The solvent was removed by reduced pressure. The desired product (**10**) (2.37 g, 50%) was obtained after purification by column chromatography (200 g, SiO_2, CH_2Cl_2:MeOH:$iPrNH_2$ 4:4:1). Tlc (CH_2Cl_2:MeOH:$iPrNH_2$ 4:4:1) R_f 0.55; ^1H nmr (400 MHz, $CDCl_3$) δ 4.21 (br s, 3 H, NH_2, NH), 2.90 -2.87 (m, 6 H, CH_2NH), 2.56 (t, 2 H, *J* = 6.78 Hz, CH_2CN), 1.58-1.56 (m, 4 H, CH_2CH_2NH); ms(CI) 159.

***N*-(Cyanoethyl)-di-BOC-1,4-butyldiamine (11).** To a 30 ml dry CH_2Cl_2 solution containing **10** (1.28 g, 9.09 mmol), was dropped di-*t*-butyl dicarbonate (4.96 g, 22.72 mmol) in 5 ml CH_2Cl_2. The reaction mixture was stirred for 5 h. After removal of the solvent, the oily product mixture was washed with H_2O (2 x 50 ml), sat. $NaHCO_3$ solution (2 x 40 ml), and brine (1 x 50 ml), and the organic layer was dried over $MgSO_4$. The desired product (**11**) (2.94 g, 95%) was obtained after purification by column chromatography (150 g, SiO_2, EtOAc:hexane 15:85). Tlc (EtOAc:hexane 1:3) R_f 0.21; ^1H nmr (400 MHz, $CDCl_3$) δ 4.60 (br s, 1H, NH), 3.41 (t, 2 H, *J* = 6.80 Hz, CH_2NH), 3.25-3.20 (m, 2 H, CH_2NH), 3.16-3.10 (m, 2 H, CH_2NH), 2.58 (t, 2 H, *J* = 6.80 Hz, CH_2CN), 1.61-1.50 (m, 4 H, CH_2CH_2NH), 1.43 (s, 9 H, BOC), 1.40 (s, 9 H, BOC); ms(CI) 342.

Di-BOC-43-amine (12). To 5 ml AcOH solution containing **11** (634.0 mg, 1.86 mmol), was added in 930 mg $Pd(OH)_2/C$. The resulting suspension was purged with H_2 (3 x 5 min), and shaked under 50 psi for 2 h. The reaction mixture was filtered through celite, and washed extensively with CH_3CN (50 ml). After removal of the organic solvent, the residue was neutralized with 1 N KOH (10 ml). The aqueous solution was extracted with CH_2Cl_2 (3 x 40 ml). The combined the organic layer was washed with brine (1 x 60 ml), dried over Na_2SO_4. Product (**12**) (536.6 mg, 85%) was obtained after column chromatography (100 g, SiO_2, CH_2Cl_2:MeOH: $iPrNH_2$ 95:5:0.5). Tlc (CH_2Cl_2:MeOH: $iPrNH_2$ 90:9:1) R_f 0.45; ^1H nmr (400 MHz, $CDCl_3$) δ 3.30-3.09 (m, 8 H, CH_2NH), 2.72-2.65 (m, 2 H, CH_2CH_2NH), 2.60-2.55 (m, 2 H, CH_2CH_2NH), 1.69-1.60 (m, 2 H, CH_2CH_2NH), 1.48 (s, 9 H, BOC), 1.44 (s, 9 H, BOC); ms (CI) 346.

***N*-(Cyanoethyl)-di-BOC-43-amine (13).** Acrylonitrile (122.9 ml, 1.19 mmol) was slowly injected to 10 ml MeOH containing (**12**) (536.6 mg, 0.99 mmol) at 0°, the mixture was stirred for 4 h. Evaporation of the solvent gave an oily residue. After purification by column chromatography (120 g, SiO_2, MeOH:CH_2Cl_2 1:9), anal. pure **13** (617.0 mg, 99%) was yielded. Tlc (MeOH:CH_2Cl_2 1:9) R_f 0.75; ^1H nmr (400 MHz, $CDCl_3$) δ 3.15-3.04 (m, 6 H, CH_2NH), 2.90 (t, 2 H, *J* = 6.80 Hz, CH_2NH), 2.62 (br s, 2 H, CH_2NH), 2.52 (t, 2 H, *J* = 6.80 Hz, CH_2CN), 1.70-1.60 (m, 2 H, CH_2CH_2NH), 1.54 -1.52 (m, 4 H, CH_2CH_2NH), 1.45 (s, 9 H, BOC), 1.44 (s, 9 H, BOC); ms(CI) 399.

***N*-(Cyanoethyl)-tri-BOC-43-amine (14).** To 10 ml dry CH_2Cl_2 of **13** (617.0 mg, 1.55 mmol) was slowly added di-*t*-butyl dicarbonate (508.2 mg, 2.33 mmol), the mixture was stirred for 3 h. After the solvent was removed by evaporation, the oily product mixture was washed with H_2O (1 x 15 ml), sat. $NaHCO_3$ solution (3 x 10 ml), and brine (1 x 20 ml). The organic extracts were dried over $MgSO_4$. The concentrated residue was purified by column chromatography (100 g,

SiO_2, EtOAc:hexane 1:3) to give anal. pure **14** (733.0 mg, 95%). Tlc (EtOAc:hexane 1:3) R_f 0.25; ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.48-3.42 (m, 2 H, $C\underline{H}_2NH$), 3.25 (t, 2 H, J = 7.21 Hz, $C\underline{H}_2NH$), 3.21-3.15 (m, 6 H, $C\underline{H}_2NH$), 2.65-2.60 (t, 2 H, J = 7.21 Hz, $C\underline{H}_2CN$), 1.75-1.70 (m, 2 H, $C\underline{H}_2CH_2NH$), 1.69-1.60 (m, 4 H, $C\underline{H}_2CH_2NH$), 1.49 (s, 9 H, BOC), 1.45 (s, 9 H, BOC), 1.44 (s, 9 H, BOC); ms(CI) 498.

Tri-BOC-433-amine (15). To **14** (1.12 g, 2.25 mmol) in 20 ml AcOH, was added 1.13 g 20% $Pd(OH)_2$/C. The reaction mixture was purged with H_2 (3 x 5 min), and shaked under 50 psi for 3 h. The black suspension was filtered through a pad of celite, and washed extensively with CH_3CN (100 ml). Removal of the solvent afforded an oily residue which was neutralized with 1 N KOH (20 ml). The aqueous solution was extracted with CH_2Cl_2 (3 x 40 ml), and the combined organic extracts were washed with brine (1 x 60 ml), and dried over Na_2SO_4. Anal. pure **15** (1.97 g, 98%) was obtained after column chromatography (200 g, SiO_2, CH_2Cl_2: MeOH:iPrNH$_2$ 90:9:1). Tlc (CH_2Cl_2:MeOH:iPrNH$_2$ 90:9:1) R_f 0.30; ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.15 (br s, 12 H, $C\underline{H}_2NH$), 2.69-2.68 (m, 2 H, $C\underline{H}_2CH_2NH$), 2.19-2.17 (m, 2 H, $C\underline{H}_2CH_2NH$), 1.75-1.60 (br m, 4 H, $C\underline{H}_2CH_2NH$), 1.49 (s, 9 H, BOC), 1.44 (s, 9 H, BOC), 1.43 (s, 9 H, BOC); ms(CI) 503.

***N*-(Cyanolethyl)-tri-BOC-433-amine (16).** Acrylonitrile (56.0 µl, 0.85 mmol) was slowly injected to 5 ml of MeOH containing **15** (0.354 g, 0.70 mmol), the reaction mixture was stirred for 4 h, the solvent was removed by evaporation. The oily residue was purified by column chromatography (100 g, SiO_2, MeOH:CH_2Cl_2 1:9), and **16** (0.330 g, 85%) was yielded. Tlc (MeOH:CH_2Cl_2 1:9) R_f 0.75; ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.18-3.10 (br m, 10 H, $C\underline{H}_2NH$), 3.05-3.01 (m, 2 H, $C\underline{H}_2NH$), 2.60 (br s, 2 H, $C\underline{H}_2NH$), 2.51 (t, 2 H, J = 6.04 Hz, $C\underline{H}_2CN$), 1.77-1.72 (m, 4 H, $C\underline{H}_2CH_2NH$), 1.60-1.51 (m, 4 H, $C\underline{H}_2CH_2NH$), 1.48 (s, 9 H, BOC), 1.45 (s, 9 H, BOC), 1.43 (s, 9 H, BOC); ms(CI) 556 .

***N*-(Cyanoethyl)-tetra-BOC-433-amine (17).** To 10 ml dry CH_2Cl_2 was added **16** (0.330 g, 0.60 mmol), and di-*t*-butyl bicarbonate (0.260 g, 1.19 mmol) in 2 ml CH_2Cl_2 was dropped in, the reaction mixture was stirred for 3 h. After the removal of the solvent, the oily product mixture was washed with H_2O (2 x 25 ml), sat. $NaHCO_3$ solution (2 x 20 ml), and brine (1 x 50 ml). Then, the organic layer was dried over $MgSO_4$, purified by column chromatography (100 g, SiO_2, EtOAc:hexane 1:3), and **17** (0.370 g, 95%) was obtained. Tlc (EtOAc:hexane 1:3) R_f 0.20; ^{1}H nmr (400 MHz, $CDCl_3$) δ *3.48-3.47 (m, 2 H, $C\underline{H}_2NH$), 3.28-3.24 (m, 2 H, $C\underline{H}_2NH$), 3.16-3.03 (br m, 10 H, $C\underline{H}_2NH$), 2.60 (br s, 2 H, $C\underline{H}_2CN$), 1.79-*1.75 (m, 4 H, $C\underline{H}_2CH_2NH$), 1.70-1.68 (m, 4 H, $C\underline{H}_2CH_2NH$), 1.48 (s, 9 H, BOC), 1.45 (s, 9 H, BOC), 1.44 (s, 9 H, BOC), 1.43 (s, 9 H); ms(CI) 656.

Tetra-BOC-4333-amine (5). To (**17**) (1.12 g, 1.70 mmol) in 20 ml AcOH, was added 0.85 mg 20% $Pd(OH)_2$/C. The reaction mixture was purged with H_2 (3 x 5 min), and shaken under 50 psi for 5 h. The black suspension was filtered through a pad of celite, and washed extensively with CH_3CN (100 ml). After evaporation of the solvent, the residue was neutralized with 1 N KOH (10 ml). Extraction of the aqueous solution with CH_2Cl_2 (3 x 50 ml), the combined the organic layer was washed with brine (1 x 60 ml), dried over Na_2SO_4. Product (**5**) (1.01 g, 91%) was obtained after column chromatography (200 g, SiO_2, MeOH:CH_2Cl_2 1:9). Tlc (CH_2Cl_2:MeOH:iPrNH$_2$ 90:9:1) R_f 0.28; ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.35-3.15 (br m, 14 H, $C\underline{H}_2NH$), 2.69-2.65 (m, 2 H, $C\underline{H}_2NH$), 1.72-1.64 (br m, 6 H, $C\underline{H}_2CH_2NH$), 1.60-1.55 (m, 4 H, $C\underline{H}_2CH_2NH$), 1.48 (s, 9 H, BOC), 1.45 (s, 9 H, BOC), 1.44 (s, 9 H, BOC), 1.43 (s, 9 H, BOC); ms(CI) 660.

***N*$^{\alpha}$,*N*$^{\delta}$,*N*$^{\omega}$-Tri-BOC-Arg-spermine amide (6).** To a 2 ml solution of CH_3CN containing **18** (30.0 mg, 63.3 µmol), CDI (11.3 mg, 69.6 µmol) was added. After stirring for 45 min, the mixture was injected to a 5 ml CH_3CN solution containing spermine (63.9 mg, 0.32 mmol) and Et_3N (44.1 ml, 0.32 mmol), and stirred for another 30 min. The solvent was removed by evaporation, and **6** (35.8 mg, 86%) was yielded after column chromatography (200 g, SiO_2, CH_2Cl_2:MeOH:iPrNH$_2$ 4:4:1). Tlc (CH_2Cl_2:MeOH:iPrNH$_2$ 4:4:1) R_f 0.35; ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.27 -3.25 (m, 4 H, $C\underline{H}_2NH$), 2.76-2.64 (m, 10 H, $C\underline{H}_2NH$), 1.68-1.50 (m, 12 H, $C\underline{H}_2CH_2NH$), 1.54 (s, 9 H, BOC), 1.48 (s, 9 H, BOC), 1.42 (s, 9 H, BOC); ms(CI) 658.

Cbz-Aminocaproic-di-BOC-spermine-*N*$^{\alpha}$,*N*$^{\delta}$,*N*$^{\omega}$-tri-BOC-Arg-spermine amide (20). To Cbz aminocaproic acid (8.43 mg, 31.8 µmol) in 5 ml CH_3CN, CDI (5.6 mg, 35 µmol) was added, and the reaction mixture was stirred for 30 min. The solution was injected to **6** (20.9 mg, 31.8 µmol) in 1 ml CH_3CN, stirring was continued for 2 h, and di-*t*-butyl bicarbonate (19 mg, 86.7 µmol) was added, the mixture was stirred for another 2 h at room temperature. The solvent was removed by reduced pressure, and the product (**20**) (19.6 mg, 56%) was obtained after column chromatography (15 g, SiO_2, MeOH:CH_2Cl_2 5:95). Tlc (MeOH:CH_2Cl_2 5:95) R_f 0.42; ^{1}H nmr (400 MHz, CD_3OD) δ 7.32 (br s, 5 H of Cbz), 5.06 (s, 2 H, $C\underline{H}_2$ of Cbz), 3.25-3.08 (m, 16 H, $C\underline{H}_2NH$), 2.19-2.11 (m, 2 H, $C\underline{H}_2CO$), 1.75-1.65 (br m, 8 H, $C\underline{H}_2CH_2NH$), 1.64-1.54 (m, 8 H, $C\underline{H}_2CH_2$), 1.52 (s, 9 H, BOC), 1.48-1.46 (m, 36 H, BOC); ms(FAB) 1106.

Aminocaproic-di-BOC-spermine-*N*$^{\alpha}$,*N*$^{\delta}$,*N*$^{\omega}$-tri-BOC-Arg-amide (7). To **20** (9.3 mg, 8.4 µmol) in 2 ml MeOH was added a catalytic amount of 10% Pd/C. The reaction mixutre was purged with H_2 (3 x 5 min), and exposed to H_2 for 8

h. Anal. pure product (**7**) (7.8 mg, 96%) was yielded after removal of the solvent and purification by column chromatography (20 g, SiO_2, CH_2Cl_2:MeOH:$iPrNH_2$ 90:9:1). Tlc (90:9:1 CH_2Cl_2:MeOH:$iPrNH_2$ 90:9:1) R_f 0.25; ^1H nmr (400 MHz, $CDCl_3$) δ 3.95-3.84 (br m, 4 H, C$\underline{H_2}$NH), 3.24 -3.19 (m, 4H, C$\underline{H_2}$NH), 3.46-3.12 (m, 8 H, C$\underline{H_2}$NH), 2.20-2.18 (m, 2 H, C$\underline{H_2}$CO), 1.80-1.70 (br m, 8 H, C$\underline{H_2}$CH$_2$NH), 1.65-1.54 (m, 8 H, C$\underline{H_2}$CH$_2$), 1.51-1.38 (m, 45 H, BOC); ms(FAB) 972.

Diaminobenzoic methyl ester (22). To 10 ml methanol in an ice-NaCl cold bath, $SOCl_2$ (0.66 ml, 9.21 μmol) was injected slowly. After 5 min, 3,5-diaminobenzoic acid (0.466 g, 3.06 mmol) was added in portion, the suspension turned dark-brown in a few minutes. The reaction mixture was stirred for 45 min, then the mixture was brought to 40°, and stirred for another 4 h. Evaporation of the solvent under reduced pressure yielded a residue, which was dissolved in water. The aqueous solution was basified with 1 N KOH, and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with brine(1 x 50 ml), dried over Na_2SO_4, and concentrated. Anal. pure product (**22**) (0.476 g, 94%) was used without purification. Tlc (CH_2Cl_2:MeOH 95:5) R_f 0.5 ^1H nmr (400 MHz, CD_3OD) δ 6.73 (d, 2 H, J = 2.12 Hz, H of Benzoic), 6.31 (t, 1 H, J = 2.12 Hz, H of Benzoic), 3.80 (s, 3 H, OC$\underline{H_3}$); ms(CI) 167.

Iminodibenzyl-5-carbonyldiaminobenzoic methyl ester (23). To 10 ml of freshly distilled CH_2Cl_2, was added **22** (28.8 mg, 0.17 mmol) and iminodibenzyl-5-carbonyl chloride (446 mg, 1.74 mmol), Et_3N (0.48 ml, 3.45 mmol) was injected, and DMAP (2.12 mg , 0.0174 mmol) was used as catalyst, the mixture was refluxed for 24 h under argon. The reaction was terminated by evaporating the solvent. The dark-reddish residue was washed with H_2O (3 x 15 ml). The combined organic extracts were washed again with brine (1 x 20 ml), and dried over Na_2SO_4. After the removal of the solvent and purification by column chromatography (SiO_2, 50g, CH_2Cl_2:MeOH 98:2), anal. pure **23** (76.0 mg, 72%) was obtained. Tlc (CH_2Cl_2:MeOH 95:5) R_f 0.3; ^1H nmr (400 MHz, CD_3OD) δ 7.73 (d, 2 H, J = 2.02 Hz, H of Benzoic), 7.57 (t, 1 H, J = 2.02 Hz, H of Benzoic), 7.42-7.40 (m, 4 H, H of dibenzyl), 7.28-7.24 (m, 12 H, H of dibenzyl), 3.80 (s, 3 H, OC$\underline{H_3}$), 3.28-3.09 (br s, 8 H, C$\underline{H_2}$C$\underline{H_2}$); ms(CI) 625.

Iminodibenzyl-5-carbonyldiamino benzoic acid (8). To a 3 ml MeOH solution of **23** (49.0 mg, 81.0 μmol), was added LiOH (18.1 mg, 430 μmol) in 1 ml H_2O. The cloudy H_2O/MeOH solution turned clear instantly when 1 ml THF was dropped in. The reaction mixture was stirred overnight at room temperature. Evaporation of the solvent afforded a solid residue, which was dissolved in water. The aqueous solution was acidified with 1 N HCl, and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with brine (1 x 25 ml), and dried over Na_2SO_4. Anal. pure **8** (47.2 mg, 98.6%) was yielded after evaporation and purification by column chromatography (30g, SiO_2, CH_2Cl_2:MeOH 98:2). Tlc (CH_2Cl_2:MeOH 95:5) R_f 0.42; ^1H nmr (400 MHz, CD_3OD): δ 7.73 (d, 2 H, J = 2.12 Hz, H of Benzoic), 7.57 (t, 2 H, J = 2.12 Hz, H of Benzoic), 7.42-7.40 (m, 4 H, H of dibenzyl), 7.28-7.20 (m, 12 H, H of dibenzyl), 3.14-2.95 (br m, 8 H, C$\underline{H_2}$C$\underline{H_2}$); ms(CI) 611.

Iminodibenzyl-5-carbonyldiaminobenzoic-spermine amide (1). To a 1 ml CH_3CN solution of **8** (11.8 mg, 20.0 μmol), CDI (3.87 mg, 24.0 μmol) was added. The mixture was stirred for 0.5 h, and spermine (20.1 mg, 99.0 μmol) in CH_3CN was dropped in. After 2 h, the reaction mixture was evaporated. Anal. pure **1** (5.4 mg, 35 %) was obtained after column chromatography (15 g, SiO_2, CH_2Cl_2:MeOH:$iPrNH_2$ 4:4:1). Tlc (CH_2Cl_2:MeOH:$iPrNH_2$ 4:4:1) R_f 0.30; ^1H nmr (400 MHz, CD_3OD) δ 7.70-7.60 (m, 3 H, H of Bz), 7.46-7.38 (m, 4 H, H of dibenzyl), 7.37-7.20 (m, 12 H, H of dibenzyl), 3.47-3.31 (m, 2 H, C$\underline{H_2}$NH), 3.26-3.12 (m, 10 H, C$\underline{H_2}$NH), 3.03-2.88 (br m, 8 H, C$\underline{H_2}$C$\underline{H_2}$), 1.99-1.86 (m, 4 H, C$\underline{H_2}$CH$_2$NH), 1.81-1.79 (m, 4 H, C$\underline{H_2}$CH$_2$NH); HRms (M + H^+, $C_{47}H_{54}N_8O_7$) calcd 778.4319, found 779.4423.

Iminodibenzyl-5-carbonyldiaminobenzoic-3334-polyamine amide (2). Following the procedure for **1**, **8** (8.2 mg, 13.8 μmol), and **5** (10.0 mg, 15.2 μmol) were converted into 15.0 mg of crude product, which was purified by pTlc (CH_2Cl_2:MeOH 95:5). BOC deprotection was performed by using 30 eq. of TFA for each BOC group in CH_2Cl_2, and stirring for 1.5 h at room temperature, giving anal. pure **2** (11.5mg, 88%). ^1H nmr (400 MHz, CD_3OD) δ 7.66-7.60 (m, 3 H, H of Benzoic), 7.43-7.34 (m, 4 H, H of dibenzyl), 7.30-7.11 (m,12 H, H of dibenzyl), 3.48-3.42 (m, 2 H, C$\underline{H_2}$NH), 3.34-3.06 (br m, 14 H, C$\underline{H_2}$NH), 2.97-2.82 (m, 8 H, C$\underline{H_2}$C$\underline{H_2}$), 2.19 -2.12 (m, 4 H, C$\underline{H_2}$CH$_2$NH), 1.97-1.90 (m, 2 H, C$\underline{H_2}$CH$_2$NH), 1.71-1.59 (m, 4 H, C$\underline{H_2}$CH$_2$NH; HRms (M + H^+, $C_{50}H_{61}N_9O_3$) calcd 835.4897, found 836.4959.

Iminodibenzyl-5-carbonyldiaminobenzoic-spermine-Arg amide (3). Following the procedure for **1**, **8** (16.3 mg, 27.5 μmol), and **6** (18.1 mg, 27.5 μmol) were converted into 30.9 mg of crude product, which was purified by pTlc (CH_2Cl_2:MeOH:$iPrNH_2$ 95:5:0.1). BOC deprotection was performed by using 30 eq. of TFA for each BOC group in CH_2Cl_2, and stirring for 1.5 h at room temperature, giving anal. pure **3** (25.7 mg, 91%). ^1H nmr (400 MHz, CD_3OD) δ 7.90 (m, 1 H, H of Benzoic), 7.58-7.55 (m, 2 H, H of Benzoic), 7.43-7.38 (m, 4 H, H of dibenzyl), 7.30-7.11 (m, 12 H, H of dibenzyl), 3.87-3.80 (m, 2 H, C$\underline{H_2}$NH), 3.48-3.37 (m, 4 H, C$\underline{H_2}$NH), 3.25-3.20 (m, 8 H, C$\underline{H_2}$NH), 3.00-2.85 (m,8 H, C$\underline{H_2}$C$\underline{H_2}$), 1.95-1.62 (m, 10 H, C$\underline{H_2}$CH$_2$NH); ms (FAB) 935.

Iminodibenzyl-5-carbonyldiaminobenzoic-C_6-spermine-Arg diamide (4). To a mixture of **7** (7.8 mg, 8.0 μmol) and **8** (5.5 mg, 9.3 μmol) in 2 ml CH_2Cl_2, DCC (1.9 mg, 9.2 μmol) was added, the mixture was stirred for 4 h. After filtration through a pad of celite, the solvent was removed, and the residue was purified by column chromatography (15 g, SiO_2, CH_2Cl_2: MeOH 98:2) to afford 2.4 mg of product, which was deprotected by using 30 eq. of TFA for each BOC group in CH_2Cl_2, stirring for 1.5 h and evaporation afforded **4** (9.8 mg, 99%). ^1H nmr (400 MHz, CD_3OD) δ 7.90 (s, 1 H, H of Benzoic), 7.56 (d, 2 H, J = 2.00 Hz, H of Benzoic), 7.44-7.40 (m, 4 H, H of dibenzyl), 7.29-7.26 (m, 12 H, H of dibenzyl), 3.87-3.75 (m, 4 H, CH_2NH), 3.25-3.11 (m, 10 H, CH_2NH), 3.01-2.95 (m, 8 H, CH_2CH_2), 2.26-2.21 (m, 2 H, CH_2NH), 1.85-1.62 (br m, 18 H, CH_2CH_2NH); ms(FAB) 1049.

5-(4'-Carboxymethylphenyl)-10,15,20-triphenylporphin (28). To a mixture of **25** (4.10 g, 25 mmol), **26** (7.96 g, 75 mmol), and $Zn(OAc)_2$ (5.480g, 25 mmol) in propionic acid (500 ml), **27** (6.71 g, 100 mmol) was added at 100° within 1 h under vigorous stirring. The resulting dark solution was refluxed for further 4 h and then cooled to room temperature. The solvent was evaporated (15 Torr, 80°), and the solid residue was subjected to column chromatography (SiO_2, 40 g, 7 x 45 cm, CH_2Cl_2); all product containing fractions were collected. The volume was reduced to 100 ml (15 Torr), then pyridine (2 ml) and an excess of DDQ (2 g) were added at room temperature. The resulting mixture was refluxed until the oxidation was complete (1 h), monitored by the disappearance of the absorption at 626 nm. Cooled to room temperature, the solution was extracted with 18% aq. *HCl* soln. (3 x 100 ml), neutralized with sat. aq. $NaHCO_3$ soln. (3 x 100 ml), washed with brine (1 x 100 ml), dried (Na_2SO_4), and evaporated (15 Torr) to give 11.5 g of black-purple crude product. Purification by column chromatography (SiO_2, 30 g, 3.5 x 30 cm, CH_2Cl_2) yielded anal. pure **28** (1.23 g, 7.5%) as deep purple crystals. Tlc (CH_2Cl_2) R_f 0.74; mp >300°; ^1H nmr (400 MHz, $CDCl_3$) δ 8.89-8.85 (m, 8 H of pyrrole), 8.46 (d, 2 H, J = 8.14 Hz, H-C(2'), -C(6')), 8.32 (d, 2 H, J = 8.14 Hz, H-C(3'), -C(5')), 8.25-8.22 (m, 6 H, H-C(2''), -C(6'')), 7.80-7.75 (m, 9 H, H-C(3''-5'')), 4.13 (s, 3 H, $COOCH_3$), -2.64 (s, 2 H, NH, exchangable with D_2O); ^{13}C nmr (300 MHz, $CDCl_3$) δ 167.35, 147.18, 142.19, 134.61, 133.91, 132.30, 131.34, 130.90, 129.72, 128.08, 127.98, 127.69, 126.77, *120.50, 118.91, 52.36; ir* (CCl_4) 1718s, *1285s; ms*(FAB) 673; HRms (M + H^+, $C_{46}H_{33}N_4O_2$) calcd 673.2603, found 673.2598; uv/vis (MeOH) 645 (4600), 588 (4500), 545 (7000), 511 (15 900), 413 (353 000), 365 (sh., 33 000); uv/vis (CH_2Cl_2) 645 (4400), 588 (4450), 545 (6900), 511 (15 700), 413 (371 000), 365 (sh., 31 500); cd (MeOH) -; cd (CH_2Cl_2)

5-(4'-Carboxyphenyl)-10,15,20-triphenylporphin (TPP, 24). To a solution of **28** (1.10 g, 1.63 mmol) in EtOH (50 ml), 2N NaOH (100 ml) was added, and the suspension was refluxed for 4 h. Cooled to room temperature, the solvent was decanted, and the solid product was washed with H_2O (2 x 50 ml), MeOH (3 x 20 ml), and hexane (2 x 50 ml). Evaporation (15 Torr and 0.01 Torr) gave anal. pure **24** (922 mg, 86%) as a deep purple powder. mp >300°; ^1H nmr (400 MHz, $CDCl_3$) δ 8.83-8.81 (m, 8 H of pyrrole), 8.51 (d, 2 H, J = 8.05 Hz, H-C(2'), -C(6')), 8.35 (d, 2 H, J = 8.05 Hz, H-C(3'), -C(5')), 8.24-8.21 (m, 6 H, H-C(2''), -C(6'')), 7.80-7.74 (m, 9 H, H-C(3''-5'')), -2.00 to -3.00 (br. m, ca. 2 H, NH, exchangable with D_2O); ir (CCl_4) 3444s, 1639s, 1211m; ms(FAB) 659; HRms (M + H^+, $C_{45}H_{31}N_4O_2$) calcd 659.2446, found 659.2457; uv/vis (MeOH) 645 (4600), 588 (4500), 545 (7000), 511 (15 900), 413 (353 000), 365 (sh., 33 000).

5-(4'-Carboxymethylphenyl)-10,15,20-tri(3''-pyridyl)porphin (29). To a mixture of **25** (4.10 g, 25 mmol), **21** (8.03 g, 75 mmol), and $Zn(OAc)_2$ (5.48 g, 25 mmol) in propionic acid (500 ml), **18** (6.71 g, 100 mmol) was added at 100° within 1 h under vigorous stirring. The resulting dark solution was refluxed for another 4 h and then cooled to room temperature. The solvent was evaporated (15 Torr, 80°), and the solid residue was subjected to column chromatography (SiO_2, 40 g, 7 x 45 cm, CH_2Cl_2:MeOH 9:1); all products containing fractions were collected. After evaporation of the solvent (15 Torr), the resulting black redidue was dissolved in CH_2Cl_2 (100 ml), pyridine (2 ml) and an excess of DDQ (2 g) were added at room temperature. This mixture was refluxed until the oxidation was complete (1 h), monitored by the disappearance of the absorption at 626 nm. Cooled to room temperature, the solution was extracted with sat. aq. $NaHCO_3$ solution (3 x 100ml), washed with brine (1 x 100ml), dried (Na_2SO_4), and evaporated (15 Torr) to give 10.3 g of black-purple crude product. Purification by column chromatography (SiO_2, 30 g, 3.5 x 30 cm, CH_2Cl_2:MeOH 9:1) yielded anal. pure **29** (993 mg, 5.4%) as brown-greenish crystals. Tlc (CH_2Cl_2:MeOH 9:1) R_f 0.53; mp >300°; ^1H nmr (400 MHz, $CDCl_3$) δ 8.9-5.4 (several m, protons of pyrrole, phenyl, and pyridyl, 4.1-3.8 (several s, $COOCH_3$);[26] ms(FAB) 738; uv/vis (MeOH) 596 (3 400), 556 (14 500), 422 (390 000); uv/vis (CH_2Cl_2) 603 (10 600), 564 (24 000), 424 (348 000); cd (MeOH) -; cd (CH_2Cl_2) -;

5-(4'-Carboxyphenyl)-10,15,20-tri(3''-pyridyl)porphin (ZnTPyP, 31). To a solution of **29** (890 mg, 1.21 mmol) in EtOH (50 ml), 2N NaOH (100 ml) was added, and the suspension was refluxed for 4 h. Cooled to room temperature, the solvent was decanted, and the solid product was washed with water (2 x 50 ml), MeOH (3 x 20 ml), and hexane (2 x 50 ml). Evaporation (15 Torr and 0.01 Torr) gave anal. pure **31** (768 mg, 88%) as a greenish brown powder. mp >300°; ^1H nmr (400 MHz, $CDCl_3$:CD_3OD 1:1) δ 8.6-7.2 (several m, protons of pyrrole, phenyl, and pyridyl);[26] ms(CI, pos. mode) 724; ms (CI, neg. mode) 722; uv/vis (MeOH): 596 (3 200), 556 (13 500), 422 (390 000).

***N*-Cbz-L-Tyr-spermine (34).** To a solution of spermine (0.621 g, 3.08 mmol) in THF was slowly added **33** (0.537 g, 1.23 mmol), resulting in the solution of a bright yellow color. After completion of the addition, the solution stirred for 6 h at room temperature. The solvent was removed by reduced pressure. Anal. pure **34** (0.486 g, 80%) was obtained by column chromatography (100 g, SiO_2, gradient from CH_2Cl_2:MeOH 9:1 to CH_2Cl_2:MeOH:iPrNH_2 85:10:5). Tlc (CH_2Cl_2:MeOH:iPrNH_2 4:4:1) R_f 0.41; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.25 (s, 5 H, H of Cbz), 7.18 (d, 2 H, J = 7.80 Hz, H-C(2'), -C(6')), 6.88 (d, 2 H, J = 7.80 Hz, H-C(3'), -C(5')), 5.11-5.06 (m, 2H, C$\underline{H}_2$ of Cbz), 4.21 (br s, 1 H, H-C(12)), 3.37-3.33(m, 2 H, $\underline{H}$-Bn), 3.29-3.12 (m, 12 H, C$\underline{H}_2$NH), 1.66-1.54 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$NH); ms(FAB) 500.

***N*-Cbz-L-Tyr-tri-Boc-spermine (35).** To a solution of **34** (1.19 g, 2.40 mmol) in CH_2Cl_2 was added di-*t*-butyl dicaronate (0.99 g, 4.54 mmol) in portion, and Et_3N (1.65 ml, 12.0 mmol) was injected. The reaction mixture was stirred for 4 h at room temperature. After extraction with sat. $NaHCO_3$ solution (3 x 50 ml), the combined organic layers were washed with brine (1 x 50 ml), dried over Na_2SO_4 , and concentrated in vacuo. Anal. pure **35** (1.4428 g, 75%) was obtained by flash chromatography (SiO_2, 250 g, CH_2Cl_2: MeOH 9:1). Tlc (CH_2Cl_2: MeOH 9:1) R_f 0.65; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.25 (s, 5 H, H of Cbz), 6.9 (d, 2 H, J = 7.80 Hz, H-C(2'), -C(6')), 6.67 (d, 2 H, J = 7.80 Hz, H-C(3'), -C(5')), 5.02 (s, 2 H, C$\underline{H}_2$ of Cbz), 4.3 (br s,1 H, H-C(12)), 3.37-3.33 (m, 2 H, $\underline{H}$-Bn), 3.30-3.08 (br s, 12 H, C$\underline{H}_2$NH), 1.65 -1.52 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$NH), 1.48 (s, 9 H, BOC), 1.46 (s, 9 H, BOC), 1.44 (s, 9 H, BOC); ms(CI) 798.

L-Tyr-tri-Boc-spermine (36). To a solution of **35** (1.44 g, 1.81 mmol) in MeOH (25 ml), a catalytic amount of 10% Pd/C was added. The mixture was purged for three times and stirred under H_2 for 8 h. Then, the suspension was filtered through celite, and MeOH was removed by reduced pressure. Anal. pure **36** (1.01 g, 84%) was obtained by flash chromatography (SiO_2, 250 g, gradient from CH_2Cl_2:MeOH 9:1 to CH_2Cl_2:MeOH:iPrNH_2 90:9:1). Tlc (CH_2Cl_2: MeOH:iPrNH_2 90:9:1) R_f 0.39; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.15 (d, 2 H, J = 7.80 Hz, H-C(2'), -C(6')), 6.80 (d, 2 H, J = 7.80 Hz, H-C(3'), -C(5')), 4.43 (br s, 1 H, H-C(12)), 3.20-2.90 (m, 12 H, C$\underline{H}_2$NH), 1.66-1.62 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$NH), 1.58-1.50 (m, 27 H, BOC); ms(FAB) 665.

6-Cbz-Hexanoyl-L-tyr-tri-Boc-spermine (37). To the mixture of **36** (0.277 g, 0.43 mmol) and Cbz-6-aminocaproic acid (0.114 g, 0.43 mmol) in CH_2Cl_2 (10 ml), was added DCC (0.102 g, 0.49 mmol). The solution was stirred under argon at room temperature for 3 h, and the white precipitate was removed by filtration through celite. The solvent was removed under reduced pressure. Pure **37** (0.34 g, 87%) was obtained by column chromatography (SiO_2, 100 g, 95:5 CH_2Cl_2:MeOH). Tlc (CH_2Cl_2:MeOH 95:5) R_f 0.26; ^{1}H nmr(400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 5 H, H of Cbz), 7.18 (d, 2 H, J = 7.8 Hz, H-C(2'), -C(6')), 6.80 (d, 2 H, J = 7.80 Hz, H-C(3'), -C(5')), 5.12 (s, 2 H, C$\underline{H}_2$ of Cbz), 4.43-4.41 (m, 1 H, H-C(12)), 3.39-3.36 (m, 2 H, $\underline{H}$-Bn), 3.21-2.90 (m, 12 H, C$\underline{H}_2$NH), 2.09-1.64 (m, 6H, C$\underline{H}_2$C$\underline{H}_2$), 1.63-1.59 (m, 8 H, C$\underline{H}_2$C$\underline{H}_2$NH), 1.58-1.50 (m, 27 H, BOC); ms(CI) 912.

***N*^{18}-Cbz-Hexanoyl-L-THP-tyr-tri-BOC-polyamine-343 (38).** To a solution of **37** (55.0 mg, 60 μmol), and PPTS (18.9 mg, 75 μmol) in dry CH_2Cl_2 (5 ml), a solution of DHP (6.3 mg, 75 μmol) in CH_2Cl_2 (1 ml) was added at room temperature. After stirring for 2 h, CH_2Cl_2 (40 ml) was added, and the reaction mixture was extracted with sat. aq. NH_4Cl solution (3 x 50 ml), neutralized with sat. aq. $NaHCO_3$ solution (3 x 50 ml), washed with brine (1 x 50ml), dried (Na_2SO_4), and evaporated (15 Torr) to give 60 mg (100%) of crude product, which was purified by column chromatography (SiO_2, 20 g, 2 x 30 cm, CH_2Cl_2: MeOH 15:1) to give anal. pure **38** (55.0 mg, 92%) as a colorless liquid. Tlc (CH_2Cl_2:MeOH 15:1) R_f 0.61; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.50-7.30 (m, 5 H of Cbz), 7.08 (d, 2 H, J = 7.77 Hz, H-C(2'), -C(6')), 6.94 (d, 2 H, J = 7.77 Hz, H-C(3'), -C(5')), 6.05-6.00 (br. m, 1 H, NH), 5.35-5.33 (t-lk m, 1 H, H-C(1) of THP), 5.13-5.09 (m, 2 H, Bn of Cbz), 4.94-4.90 (m, 1 H, NH), 4.68-4.63 (m, 2 H, H-Bn), 3.93-3.84, 3.61-3.54 (2m, 2 H, H-C(3) of THP), 3.32-2.95 (m, 15 H, H-C(1, 3, 4, 7, 8, 10, 12, 18)), 2.26-2.11 (m, 2 H, H-C(14)), 2.03-1.20 (m, 20 H, H-C(2, 5, 6, 9, 15-17, 4-6 of THP)); 1.46, 1.44, 1.42 (3s, 27 H, 3 x BOC); ms(CI) 1014 (M + NH_4^+).

***NH*$_2$^{18}-Hexanoyl-L-THP-tyr-tri-BOC-polyamine-343 (32).** A suspension of **38** (40.8 mg, 41 μmol), and excess of 10% Pt/C in dry MeOH (3 ml) was exposed to H_2 for 8 h at room temperature. The reaction mixture was filtered and washed through a pad of celite, and the solvent was evaporated (15 Torr) to give an oily crude product. Purification by column chromatography (SiO_2, 20 g, 2 x 30 cm, CH_2Cl_2:MeOH:isopropylamine 8:2:0.01) afforded anal. pure **32** (26.8 mg, 76%) as a colorless oil. Tlc (CH_2Cl_2:MeOH:iPrNH_2 8:2:0.01) R_f 0.65; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.11 (d, 2 H, J = 7.16 Hz, H-C(2'), -C(6')), 7.09 (d, 2 H, J = 7.16 Hz, H-C(3'), -C(5')), 6.13-6.06 (br. m, 1 H, NH), 5.35-5.33 (t-lk m, 1 H, H-C(1) of THP), 5.31-5.26 (m, 1 H, NH), 4.68-4.60 (m, 2 H, H-Bn), 3.93-3.82, 3.61-3.53 (2m, 2 H, H-C(3) of THP), 3.32-2.95 (m, 15 H, H-C(1, 3, 4, 7, 8, 10, 12, 18)), 2.26-2.11 (m, 2 H, H-C(14)), 2.03-1.20 (m, 20 H, H-C(2, 5, 6, 9, 15-17, 4-6 of THP)); 1.46, 1.44, 1.42 (3s, 27 H, 3 x BOC); ms(CI) 863.

***N*^{18}-TPP-Hexanoyl-L-THP-tyr-tri-Boc-polyamine-343 (39).** To a solution of **24** (12.3 mg, 8.2 μmol), EDC (3.8 mg, 20 μmol), and DMAP (2.2 mg, 20 μmol) in dry CH_2Cl_2 (1 ml), a solution of **38** (13.0 mg, 15.1 μmol) in dry CH_2Cl_2 (1 ml) was added at room temperature. The reaction mixture was stirred overnight at room temperature; then CH_2Cl_2 (20 ml)

was added. The solution was extracted with sat. aq. NH_4Cl solution (3 x 20 ml), washed with brine (1 x 20 ml), dried (Na_2SO_4), and evaporated (15 Torr) to give a purple crude product. Purification by column chromatography (SiO_2, 20 g, 2 x 30 cm, CH_2Cl_2:MeOH 15:1) afforded anal. pure **39** (12.3 mg, 54%) as a puple powder. Tlc (CH_2Cl_2:MeOH 9:1) R_f 0.50; ^1H nmr (400 MHz, $CDCl_3$) δ 8.84-8.82 (m, 8 H of pyrrole), 8.77 (d, 2 H, J = 8.00 Hz, H-C(2", 6")), 8.67-8.63 (m, 6 H, C(2"', 6"')), 8.49 (d, 2H, J = 8.00 Hz, C-H(3", 5")), 8.21-8.17 (m, 9 H, H-C(3"'-5"')), 7.11 (d, 2 H, J = 7.10 Hz, H-C(2'), -C(6')), 6.93 (d, 2 H, J = 7.10 Hz, H-C(3'), -C(5')), 6.93-6.87 (m, 1H NH), 6.08 - 6.04 (m, 1H, NH), 5.26-5.23 (m, 1 H, H-C(1) of THP), 4.64-4.55 (m, 2 H, H-Bn), 3.93-3.86, 3.48-3.40 (2m, 2 H, H-C(3) of THP), 3.59- 3.57 (m, 2 H, H-C(18)), 3.30-2.80 (m, 13 H, H-C(1, 3, 4, 7, 8, 10, 12)), 2.30-2.19 (m, 2 H, H-C(14)), 2.03-1.20 (m, 20 H, H-C(2, 5, 6, 9, 15-17, 4-6 of THP)); 1.46, 1.44, 1.42 (3s, 27 H, 3 x BOC), -2.79 (s, 2 H); ms(FAB) 1504; uv/vis (CH_2Cl_2) 645 (4400), 588 (4450), 545 (6900), 511 (15 700), 413 (371 000), 365 (sh., 31 500).

***N*^{18}-TPP-Hexanoyl-L-tyr-polyamine-343 (40).** To a solution of **39** (12.3 mg, 8.2 μmol) in dry CH_2Cl_2, *ca.* 30 eq. of TFA were added. The resulting green solution was stirred at room temperature until it became colorless and a green solid precipitated (1 h). The solvent was removed (15 Torr), and the green solid was dissolved in a solution of TFA (ca. 30 eq.) in dry EtOH (2 ml), and stirred overnight at room temperature. Evaporation of the solvents (15 Torr and 0.01 Torr) afforded anal. pure **40** (13.3 mg, 96%) as a green solid. Tlc (RP-18, MeOH:TFA 25:1) R_f 0.38; ^1H nmr (400 MHz, CD_3OD)[27] δ 8.93 - 8.85 (m, 8 H of pyrrole), 8.71 (d, 2 H, J = 8.00 Hz, H-C(2", 6")), 8.67-8.59 (m, 6 H, C(2"', 6"')), 8.51 (d, 2H, J = 8.00 Hz, C-H(3", 5")), 8.15-8.03 (m, 9 H, H-C(3"'-5"')), 7.09 (d, 2 H, J = 7.14 Hz, H-C(2'), -C(6')), 6.72 (d, 2 H, J = 7.14 Hz, H-C(3'), -C(5')) 4.45 (dd-lk m, 2 H, H-Bn), 3.56 (t-lk m, 2 H, H-C(18)), 3.27-3.25 (m, 2 H, H-C(10)), 3.13-3.11 (m, 2 H, H-C(3)), 3.11-3.09 (m, 2H, H-C(1)), 3.08-3.06 (m, 2 H, H-C(8)), 3.04 - 3.02 (m, 2 H, H-C(7)), 3.04-2.89 (br. m, 1 H, H-C(12)), 2.85 (t-lk m, 2 H, H-C(4)); 2.32 (t-lk m, 2 H, H-C(14)), 2.10 (m, 2 H, H-C(2)), 1.78-1.76 (m, 6 H, H-C(5, 6, 17)), 1.76-1.74 (m, 2 H, H-C(9)), 1.71-1.69 (m, 2 H, H-C(15)), 1.47-1.44 (m, 2 H, H-C(16)); ms(FAB) 1119; HRms (M + H^+, $C_{70}H_{75}N_{10}O_4$) calcd 1119.5970, found 1119.5946; uv/vis (MeOH) 645 (1 700), 589 (5 300), 544 (6 300), 513 (13 800), 414 (380 000); uv/vis (buffer B) 648 (2 700), 593 (4 800), 556 (7 900), 520 (16 900), 422 (142 300), 410 (138 300); cd (MeOH) -; cd (buffer B) 439 (-3.2), 431 (0), 415 (+2.9).

***N*^{18}-ZnTPyP-Hexanoyl-L-THP-tyr-tri-Boc-polyamine-343 (41).** To a solution of **31** (1.0 mg, 1.33 μmol), EDC (0.7 mg, 3.7 μmol), and DMAP (0.4 mg, 3.7 μmol) in dry CH_2Cl_2 (1ml), a solution of **32** (1.0 mg, 1.16 μmol) in dry CH_2Cl_2 (1ml) was added at room temperature. The reaction mixture was stirred overnight at room temperature; then CH_2Cl_2 (20ml) was added, the solution was extracted with sat. aq. NH_4Cl solution (3 x 20ml), washed with brine (1 x 20ml), dried (Na_2SO_4), and evaporated (15 Torr) to give a green-brown crude product. Purification by pTlc (SiO_2, CH_2Cl_2: MeOH 9:1) afforded anal. pure (**41**) (1.1 mg, 61%) as a brown powder. Tlc (CH_2Cl_2:MeOH 9:1) R_f 0.43 (side product: 0.51); ^1H nmr (400 MHz, $CDCl_3$)[26] δ 9.0-7.6 (br. m, H of ZnTPyP), 7.1-6.9 (m, H-C(2'-6')), 5.3-5.2 (m, H-C(1) of THP), 4.7 - 4.5 (m, H-Bn), 3.9-3.4 (m, H-C(3) of THP), 3.3-2.8 (m, H-C(1, 3, 4, 7, 8, 10, 12, 18)), 2.3-2.1 (m, H-C(14)), 2.0-1.2 (m, H-C(2, 5, 6, 9, 15-17, 4-6 of THP)); 1.46, 1.44, 1.42 (3s, 27 H, 3 x BOC); ms(FAB) 1606 (50, M + K^+), 1592 (100, M + Na^+), 1568 (80, M + H^+); uv/vis (CH_2Cl_2) 603 (10 600), 564 (24 000), 424 (348 000).

***N*^{18}-ZnTPyP-Hexanoyl-L-tyr-polyamine-343 (42).** To a solution of **41** (1.1 mg, 0.7 μmol) in dry CH_2Cl_2, *ca.* 30 eq. of TFA were added. The resulting green solution was stirred at room temperature until it became colorless and a green solid precipitated (1 h). The solvent was removed (15 Torr), and the green solid was dissolved in a solution of TFA (*ca.* 30 eq.) in dry EtOH (2 ml), and stirred overnight at room temperature. Evaporation of the solvents (15 Torr and 0.01 Torr) afforded anal. pure **42** (0.83 mg, 99%) as a green solid. Tlc (RP-18, MeOH:TFA 25:1) R_f 0.55; ^1H nmr (400 MHz, CD_3OD) δ 9.49-9.40 (m, 3 H, H-C(2"')), 9.11-9.08 (m, 3 H, H-C(4"')), 9.05-8.80 (m, 8 H of pyrrole), 8.91-8.84 (m, 3 H, H-C(6"')), 8.38-8.22 (m, 4 H, H-C(2", 3", 5", 6")), 8.10-8.01 (m, 3 H, H-C(5"')), 7.10-7.03 (m, 2 H, H-C(2'), -C(6')), 6.75 - 6.68 (m, 2 H, H-C(3'), -C(5')), 4.48-4.40 (m, 2 H, H-Bn), 3.60-3.50 (m, 2 H, H-C(18)), 3.27-2.89 (m, H-C(1, 3, 7, 8, 10, 12)), 2.89-2.85 (m, 2 H, H-C(4)); 2.34 -2.30 (m, 2 H, H-C(14)), 2.11-2.07 (m, 2 H, H-C(2)), 1.93-1.69 (m, 10 H, H-C(5, 6, 9, 15, 17)), 1.47-1.44 (m, 2 H, H-C(16)); ms(FAB) 1185; uv/vis (MeOH) 595 (3 400), 557 (15 600), 422 (380 000) 403 (sh., 44 000); uv/vis (buffer B) 606 (7 300), 566 (12 000), 433 (116 300), 421 (107 400); cd (MeOH) -; cd (buffer B) 451 (+2.8), 440 (0), 434 (-3.1), 418 (0), 409 (+0.6).

***N*^{18}-TPyP-Hexanoyl-L-tyr-polyamine-343 (43).** A solution of conc. HCl (0.3 ml) in MeOH (0.6 ml) was added to solid (**42**) (0.83 mg, 0.7 μmol), and without stirring the solvent was evaporated (15 Torr) immediately yielding a green crude product, which was chromatographed (SiO_2, RP-18, 10 g, MeOH:TFA 100:1) to give quantitatively anal. pure **43** (0.75 mg) as a deep green powder. Tlc (RP-18, MeOH:TFA 25:1) R_f 0.60; ^1H nmr (400 MHz, CD_3OD) δ 9.73-9.69 (m, 3 H, H-C(2"')), 9.31-9.29 (m, 6 H, H-C(4"', 6"')), 9.05-8.80 (m, 8 H of pyrrole), 8.44 -8.41 (m, 3 H, H-C(5"')), 8.38 -8.32 (m, 4 H, H-C(2", 3", 5", 6")), 7.10 (d, 2 H, J = 7.85 Hz, H-C(2'), -C(6')), 6.73 (d, 2 H, J = 7.85 Hz, H-C(3'), -C(5')), 4.48-4.40 (m, 2 H, H-Bn), 3.60-2.89 (m, H-C(1, 3, 7, 8, 10, 12, 18)), 2.92-2.87 (m, 2 H, H-C(4)); 2.31-2.26 (m, 2 H, H-C(14)), 2.11-2.07 (m, 2 H, H-C(2)), 1.93-1.69 (m, 10 H, H-C(5, 6, 9, 15, 17)), 1.47-1.44 (m, 2 H, H-C(16)); ms(FAB) 1121; uv/vis (MeOH) 645 (1 600), 589 (5 200), 544 (6 100), 513 (13 000), 414 (370 000); uv/vis (buffer B) 649 (6 400), 592 (11 200), 555 (15 600), 520 (29 700), 415 (247 300); cd (MeOH) -; cd (buffer B) 440 (-0.9), 418 (-0.6), 410 (-0.7).

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Abbreviations: BOC: *tert*-butoxycarbonyl; buffer B: 100 mM NaCl, 10 mM Na_2HPO_4, 1 mM EDTA, 125 mM PMSF, 0.02% NaN_3; Cbz: carbobenzoxy; DCC: dicyclohexylcarbodiimide; DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; DMAP: N,N'-dimethyl-4-aminopyridine; CDI: N,N'-carbonyldiimidazole; EDC: 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide; TFA: trifluoroacetic acid.

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26. Due to intermolecular pyridine zinc complex formation the assignements of the resulting broad and/or upfield shifted signals is not clear.
27. The assignements of the PhTX signals was done by a 400 MHz ^1H nmr 2D COSY spectrum. Other polyamine spectra were interpertated based on this assignements.

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